

CARDIAC RESPONSE TO CIRCULATING FACTORS
IN ENDOTOXIN SHOCK

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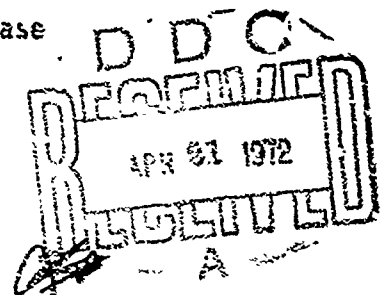
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<p>Findings from the literature suggest the presence of a deleterious factor in the blood of endotoxin-shocked animals. The purpose of the present study was to explore the possibility that myocardial performance is adversely affected by circulating substances released from distant sites and transmitted to the heart via the blood. Experiments were carried out on adult mongrel dogs administered endotoxin. Blood from these animals was subsequently perfused through an isolated working left ventricle from a donor animal. Results show that after 6-9 hours following injection of endotoxin, cardiac performance is normal in comparison to control experiments. Performance curves elicited by altering mean aortic pressure (afterload) from 75-150 mm Hg revealed no important differences between endotoxin and control groups in stroke work, power, dp/dt, left ventricular end diastolic pressure, O_2 uptake and CO_2 production, coronary flow and resistance. Performance curves demonstrated normal myocardial function even during terminal stages of shock. Results indicate that if deleterious agents are circulating in the blood from endotoxin-treated animals, they do not depress myocardial function.</p>			

UNIVERSITY OF OKLAHOMA MEDICAL CENTER

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Introduction

Evidence for the presence of a circulating toxin or depressant substance has been previously described by Cannon (6), Shorr and colleagues (22, 23), and more recently by others (12, 13, 16, 28, 29) including Lefer, with the introduction of the "myocardial depressant factor" (12, 13, 28, 29). The significance of such substances cannot be overestimated, particularly in regard to their possible adverse effects on myocardial performance in shock. On the other hand, changes in venous return may indirectly alter cardiac output. Evidence for decreases in venous return elicited by peripheral vascular mechanisms in early shock is convincing (9, 30), however, no suitable information is presently available to explain the mechanism of the depression of cardiac output in the intermediate stage of shock. Research from this laboratory (10) and others (8, 14) has strongly suggested that the myocardium performs normally in the early phase of endotoxin shock (0-4 hours). No adverse effects on myocardial work performance, metabolism or hemodynamics were observed even in the case of early death. It was the intention of the present investigation to extend the period of observation to from nine to twelve hours after endotoxin administration and to explore the possibility of a circulating factor deleterious to myocardial performance. Results indicate no adverse cardiac response to circulating blood from animals in the intermediate or terminal stages of shock.

Methods

Experiments were conducted on adult mongrel dogs intravenously anesthetized with sodium pentobarbital, 30 mg/kg. The basic procedure included isolating a left ventricle and supporting it with blood exchanged with a heparinized support animal as shown in Figure 1, as previously reported (10).

In the experimental group (N = 8) six hours prior to heart transfer, E. coli endotoxin (Difco, Detroit), was injected intravenously into the support dog. A mean shocking dose of endotoxin, 0.4 mg/kg (range 0.3-0.7), was selected by using a group of 32 animals in which 14 or 44% had died within six hours. The heart donor dogs for the experimental group were not given endotoxin. In the control experiments (N = 10) neither the support dogs nor the heart donor animals were given endotoxin.

During the equilibration period of the isolated heart, aortic pressure was adjusted to 100 mm Hg and cardiac output was set at 76 cc/min/kg body weight (based on the weight of the heart donor dog). These pressure and flow values supported and maintained left ventricular systolic and diastolic pressure, coronary blood flow, and myocardial oxygen uptake in the physiological range. Further, the mean coronary arterial pressure (afterload) of the isolated heart was adjusted to these following pressures after 100 mm Hg: 125, 150, and again 100 mm Hg. These pressures were changed and stabilized by adjusting a screw clamp located on the aortic outflow as cardiac output and blood temperature were held constant and arterial and venous blood samples were taken, cardiac performance, metabolic and hemodynamic parameters could be evaluated at each separate afterload. In addition a short pressure/flow curve was included between the coronary pressures of 125 and 150 mm Hg.

For the curve, cardiac output was constant but the screw clamp was quickly adjusted to produce the following coronary pressures: 75, 100, 125, 150 and 75 mm Hg. At each pressure change cardiac performance and hemodynamics could be evaluated. This procedure was included to avoid possible spontaneous changes during a longer time period and to more readily compare changes in cardiac performance and hemodynamics as functions of afterload in control and experimental groups. All parameters reported in the study were of a steady state nature as defined by constant values of coronary pressure, coronary blood flow, cardiac output and dp/dt .

Coronary arterial and venous PO_2 , PCO_2 and pH were followed by utilizing an Instrumentation Laboratories blood gas analyzer calibrated prior to each determination with known gas mixtures. Oxygen content of coronary arterial and venous blood was measured by a Van Slyke manometric blood gas analyzer. Blood temperatures in the heart were maintained relatively constant within each experimental group by appropriate adjustments of water bath and heating pad temperatures. Simultaneously obtained coronary blood flow measurements permitted the calculation of oxygen uptake and carbon dioxide production from the product of coronary flow and A-V oxygen or carbon dioxide differences.

Stroke work in gram-meters was calculated from the formula used by others (18):

$$(MAP - LVEDP) (SV) (1.36)/100$$

where MAP = mean aortic pressure (mmHg); LVEDP = left ventricular end diastolic pressure (mmHg) and SV = stroke volume in cc, determined by dividing cardiac output by heart rate. The acceleration component of left ventricular stroke work was disregarded in the calculations on the basis that it represents less than 1 per cent of total stroke work (19).

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Cardiac power was calculated and expressed as work per second. The maximum change in pressure (dP/dT) occurring during isometric contraction of the left ventricle was continuously recorded and expressed as the first derivative of the pressure rise. Calibration of the dP/dT recording was carried out by analysis of the slope of a line drawn tangentially to the steepest portion of the left ventricular isovolumetric tracing and expressed as mm Hg/sec (10).

Electrocardiograms were obtained by placing the ground lead into the moist tissue surrounding the trachea, Lead 1 into the left ventricular myocardium adjacent to the lower edge of the left atrium and Lead 2 into myocardium at the apex of the left ventricle.

Coronary blood flow averaged 115 and 135 cc/min/100 gms left ventricle at the first 100 mm Hg coronary pressure in the controls (N = 10) and experimentals (N = 8) respectively. Oxygen uptake was assumed to be negligible in atria and right ventricle (bypassed) as was reported by others (21) and averaged 9.04 and 12.10 cc/min/100 gms left ventricle at the first 100 mm Hg afterload in the controls (N = 10) and experimentals (N = 8) respectively.

The body weight of both experimental and control support animals averaged 22.31 (± 0.55) kilograms. The mean body weight and left ventricular weight for heart donors in both experimental and control groups were 5.28 (± 0.15) kilograms and 33.28 (± 1.94) grams respectively.

Results

Typical findings obtained in a control isolated heart preparation are characterized in Figure 2. Figure 2a represents coronary pressure sustained for extended periods so that simultaneous arterial and venous samples could be taken. Figure 2b represents a pressure/flow curve with

afterloads of short duration. The total time involved was 105 minutes. Cardiac output was maintained constant by a pressure-independent pump delivering blood to the pulmonary artery. The record exhibits no significant differences in the response of any parameter of the various measurements and calculations of performance and metabolic characteristics from those of the endotoxin groups.

The format of the experimental group included injecting the support dog with endotoxin 6 hours prior to transfer of an isolated heart from a control animal. Figure 3 demonstrates the typical findings obtained in an isolated heart preparation in which the support dog has been injected with endotoxin. Figure 3a represents the extended afterloads and Figure 3b the shortened periods of altered coronary pressures. The time period from the first blood sample to the last was 91 minutes. This record reveals that endotoxin has no adverse effects on myocardial performance, including dP/dT_{max} (mm Hg/sec) or power (work/sec), and does not alter the metabolic parameters of oxygen uptake and carbon dioxide production. Results clearly illustrate the important effects of coronary pressure on dP/dT , coronary flow, LVEDP, Power, O_2 uptake and CO_2 production. Notable findings from this record include the marked increases in coronary blood flow.

Figure 4 illustrates the record of an isolated heart preparation in which the support animal died immediately after the first blood sample was drawn. Results strikingly demonstrate that even when the support animal is in the terminal stages of endotoxin shock, the heart performs normally. No deleterious action can be seen in either the performance or the metabolic parameters, in comparison to control experiments.

Figure 5 shows the effects of endotoxin on mean values for coronary flow and coronary resistance in control and endotoxin isolated working heart preparations. These hemodynamic parameters were evaluated at various controlled coronary pressures (afterloads) as follows: 75, 100, 125, 150 mm Hg. The afterloads shown on the left were changed and stabilized over longer periods (mean 81 minutes) than those on the right (approximately 15 minutes). The purpose of the initial curve was to allow enough time at each afterload for simultaneous arterial and venous samples to be drawn, so that in addition to hemodynamics and performance, the metabolic processes of the heart could be evaluated. The second pressure/flow curve was done to assay hemodynamics and performance before possible spontaneous changes could occur in the heart. Final bracketing afterloads were carried out in both curves to test possible alterations in the heart during the separate maneuvers. Coronary flow changes were insignificant ($p > 0.05$) between control and experimental groups in both curves. Coronary flows rose notably with increasing afterloads in each curve. Coronary resistance decreased within the first curve, but remained relatively constant during the short pressure/flow curve.

Figure 6 summarizes mean values for dP/dT_{\max} , stroke work (SW), heart rate (HR), power (P) and left ventricular end diastolic pressure (LVEDP) in both control and endotoxin shock experiments. The mean values \pm SE of the experimental group for these parameters in the first curve at the initial 100 mm Hg and peak 150 mm Hg respectively are as follows: $dP/dT_{\max} = 2853 \pm 275.00, 4597 \pm 243.00$; SW $3.69 \pm 0.17, 5.05 \pm 0.28$; HR $151 \pm 4.89, 169 \pm 5.95$; P $9.22 \pm 0.23, 14.13 \pm 0.45$; and LVEDP $+2.9 \pm 0.9, +2.9 \pm 0.6$. The mean value for the second curve at initial 75 mm Hg and 150 mm Hg are as follows: $dP/dT_{\max} = 2334 \pm 307.00, 4279 \pm 267.00$;

SW 2.73 ± 0.16 , 5.18 ± 0.26 ; HR = 157 ± 6.62 , 163 ± 6.55 ; P = 7.03 ± 0.22 , 13.92 ± 0.41 ; and LVEDP = $+1.9 \pm 0.6$, $+3.0 \pm 0.8$. All changes in these parameters are similar in control and experimental groups with exceptions at 150 mm Hg and 100 mm Hg as follows: HR ($p < 0.05$) at both afterloads.

Results demonstrate that as afterload is increased the various performance characteristics of the heart including dF/dT_{max} , stroke work and power rise. These parameters increase regardless of the presence or absence of endotoxin. Alterations in LVEDP appear to be different between the control and experimental groups but these differences are statistically insignificant. Lower LVEDP's and increased heart rates in the experimental animals may be the result of catecholamine release from the shocked support animals.

Figure 7 demonstrates the effects of endotoxin on oxygen uptake, carbon dioxide production and the resultant RQ. Findings clearly illustrate that as the afterload rises O_2 uptake and CO_2 production increase. Differences in O_2 uptake between control and experimental and CO_2 production in the two groups are insignificant, with one exception as follows: ($p < 0.01$) between experimental and control groups, for O_2 uptake at the first 100 mm Hg reading. Blood samples were not taken during the short pressure/flow curve so metabolic evaluation of the heart was made only at each extended afterload. Mean RQ values at 100, 125, 150 and 100 mm Hg in the endotoxin group are 0.83, 0.85, 0.76, 0.90 and in the control groups are 0.86, 0.86, 0.87, and 0.97. There were no significant changes in RQ values.

Discussion

The primary purpose of the present study was to determine if toxic or myocardial depressant substances circulate in the blood of animals in the intermediate stages of endotoxin shock.

A donor heart from an animal not receiving endotoxin served as the test organ to receive blood from a previously shocked support dog. Experiments were designed to assay the myocardial effects of factors in the blood during the intermediate or terminal stages of shock. The dose of endotoxin was adjusted so that approximately forty per cent of all animals had expired at the time of the heart donor transfer (5-6 hours). It seemed reasonable that this arrangement of both time and degree of lethality should be adequate in order to reveal the net effects of possible detrimental and/or beneficial blood borne agents on myocardial performance.

Experiments carried out during the period 6-9 hours after endotoxin, including studies in which two endotoxin-treated support animals expired during the assays of myocardial performance, metabolism and hemodynamics, revealed no detrimental cardiac actions in the test organ. Changes in mean aortic pressure (afterload) through the range from 75-150 mm Hg, demonstrated that the responses of hearts receiving blood from animals in shock or controls, were in general, indistinguishable. All individual hearts in both groups demonstrated notable increases in dP/dT , left ventricular systolic pressure, coronary blood flow, stroke work, power, oxygen uptake and carbon dioxide production as functions of elevated afterload. In contrast, LVEDP changed little during the range of afterload from 75-150 mm Hg. LVEDP rose transiently during the initial increase in afterload, but decreased within 30-60 seconds to occupy a steady state value little changed from the previous coronary pressure (homeometric autoregulation). Mean changes in dP/dT , stroke work, power (work/second), LVEDP, O_2 uptake CO_2 production, coronary blood flow and coronary vascular resistance, were nearly identical or very similar, in both groups.

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Statistical differences between controls and experimental groups were seen only in heart rate at 150 and 100 mm Hg ($p < 0.05$) and oxygen uptake ($p = 0.01$) at 100 mm Hg. Hearts receiving blood from endotoxin-injected animals appeared to have slightly higher rates with somewhat greater oxygen assimilation. Also, mean LVEDP's were slightly lower at all points in the endotoxin group although differences were statistically insignificant. These latter trends are consistent with the probability that the heart is driven by humoral adrenergic influences of a beneficial nature in the intermediate stage of shock as has been suggested by Goodyer (8).

These findings offer no evidence of a circulating toxic or depressant substance damaging to the myocardium as has been described or suggested by others (12, 13, 28, 29). A number of years have passed since the classic descriptions of Cannon (6) Shorr and others (22, 23), of circulating toxic or vasodepressant factors, though the former (6) believed that the heart escaped injury from such substances even in the terminal stage of shock (Chapter IV, "The Question of a Cardiac Factor"). Clearly, however, the present experiments examine only the net effects of "shocked blood" on the heart, as indeed there may be both stimulatory and depressant influences impinging their effects simultaneously on the myocardium, with the resultant cancellation of each separate effect. Recent studies in this laboratory, however, have revealed no myocardial depressant action after endotoxin with beta adrenergic blockade (propanolol) in the early stage of shock (unpublished observations). Other findings strongly suggest that the myocardium is resistant to endotoxin (10, 14, 17, 30) affected adversely only as a terminal event (6, 11).

The possible presence of circulating myocardial depressant agents is of utmost concern in the study of the pathogenesis of septic shock. The present study and an earlier report from this laboratory (10) suggest that the endotoxin moiety itself possesses no direct myocardial toxic characteristics, and that if deleterious agents are circulating in the blood from an endotoxin-treated animal, they do not depress myocardial function, even in terminal shock.

The problem of the precise role of the heart in the development of irreversible endotoxin shock is complicated by events occurring in the periphery which indirectly influence cardiac output by decreasing venous return (9, 30). Myocardial damage or depression has been reported in animal experiments after endotoxin (13, 27) following hemorrhage (25, 26, 29), and in clinical septic shock (3, 24). Observations from certain patient populations are also suggestive of left ventricular decompensation in later stages of septic shock (15). A possible explanation of apparent differences between these previous reports and the present study is that the combined cardiac effects of a hemodynamic insult depressing myocardial blood flow (1, 2, 20), a neural dysfunction resulting from cerebral hypoxia (4), interference with cellular metabolism due to a primary toxic defect (31) or coronary vascular obstruction (7), and the circulation of abnormal products of metabolism (25-28), may all act in concert to ultimately destroy normal cardiac integrity.